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Diagnostic Strategies for Acute Febrile Illness in Indian Tertiary Care Hospitals: Current Challenges and Future Directions

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Abstract
Acute febrile illness (AFI) is a common clinical presentation, characterized by a sudden onset of fever lasting up to two to three weeks. Diagnosing AFI remains a significant challenge in Indian tertiary care hospitals due to the wide range of possible etiologies, overlapping symptoms, and limited access to specific diagnostic tools. This review explores current diagnostic approaches, with emphasis on the use of clinical markers such as differential white blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin. While these markers assist in differentiating bacterial from non-bacterial causes, their specificity in low-resource settings remains limited. The review also highlights opportunities for improving diagnostic accuracy through point-of-care testing and integrated diagnostic systems. Advancements in host biomarkers and multiplex diagnostics could potentially enhance the timely identification and management of AFI in endemic regions.
Keywords: *Acute Febrile Illness, C-reactive protein, procalcitonin, point-of-care testing, tertiary care.*

INTRODUCTION

Acute febrile illness (AFI) is a clinical syndrome characterized by a sudden onset of fever lasting less than two to three weeks and is often accompanied by non-specific symptoms such as headache, myalgia, and malaise. In tropical and subtropical countries like India, AFI is one of the most common reasons for hospital admissions and outpatient visits [1]. The etiological spectrum of AFI includes a wide range of infectious diseases such as malaria, dengue, typhoid fever, leptospirosis, scrub typhus, and viral illnesses, many of which share overlapping clinical presentations, making early diagnosis particularly challenging [2].

In Indian tertiary care settings, the diagnostic complexity is compounded by limited access to reliable laboratory infrastructure, particularly in rural or resource-constrained regions. As a result, clinicians often initiate empirical antimicrobial therapy prior to confirmation of the underlying cause, increasing the risk of antimicrobial resistance and suboptimal outcomes [3]. Conventional diagnostic methods such as complete blood counts, peripheral smear microscopy, Widal test, and rapid diagnostic kits are routinely used, but many of these tools suffer from poor sensitivity and specificity, particularly in differentiating between bacterial and viral infections [4].

To enhance diagnostic precision, recent studies have explored the utility of host-based biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), and erythrocyte sedimentation rate (ESR). For example, in a North Indian tertiary hospital cohort, CRP and ESR were found to be effective adjuncts in characterizing febrile illness patterns and guiding early intervention [1]. Similarly, PCT has shown promise in distinguishing bacterial from fungal or viral etiologies, especially among immunocompromised or critically ill patients [5]. Comparative studies conducted in Southeast Asia have also demonstrated that CRP offers greater diagnostic accuracy (AUROC 0.89) compared to PCT (AUROC ~0.78) in differentiating dengue from bacterial infections [6].

The diagnostic burden is further aggravated by co-endemic infections, seasonal variability, and healthcare inequities across regions. These challenges underscore the need for context-appropriate strategies, including point-of-care diagnostics, integrated multiplex testing, and biomarker-informed treatmentathways [7]. Improved diagnostic specificity will not only enable timely therapeutic decisions but also aid in public health surveillance and resource-allocation.

This article critically evaluates diagnostic approaches for acute febrile illness in Indian tertiary care hospitals, emphasizing conventional and emerging tools, current challenges, and future directions for strengthening clinical diagnostics.

METHODS

A targeted literature search was conducted using PubMed, Scopus, and SpringerLink databases to identify relevant articles published between 2010 and 2024, with emphasis on recent studies from the past five years. The search terms included combinations of: "acute febrile illness," "diagnosis," "biomarkers," "C-reactive protein," "procalcitonin," and "India."

Only peer-reviewed articles written in English and focusing on diagnostic approaches for AFI in Indian or comparable tropical settings were included. Studies discussing clinical features, host biomarkers, diagnostic tools, and implementation challenges in tertiary care hospitals were prioritized. Reference lists of key articles were also screened to ensure comprehensive coverage.

Etiology & Clinical Features

In Indian tertiary care hospitals, acute febrile illness (AFI) commonly presents as acute undifferentiated febrile illness (AUFI), where diagnosis often relies on epidemiology and clinical patterns. A large prospective observational study in Northern India (April 2022–March 2024) involving 4,200 AUFI/AES patients revealed the most frequent bacterial etiologies were scrub typhus (24.6%) and leptospirosis (12.4%), while dengue (23.0%) predominated among viral infections [8]. These findings highlight the shifting etiology landscape and the critical need for region-specific diagnostic strategies.

In central and southern India, similar patterns emerge. A study in central India (n = 270) found scrub typhus (47%), dengue (17.4%), malaria (12%), and enteric fever (4%) among confirmed AFI cases; notably, approximately 6.7% remained undiagnosed (Patil & Agrawal, 2017). Likewise, a multisite study in Kerala reported dengue as the leading cause (43.5%), followed by enteric fever, leptospirosis, and malaria, with nearly 30% of cases remaining indeterminate [9,10].

In pediatric populations, scrub typhus has emerged as an important etiologic agent. For example, among 613 children aged 3 months to 12 years with AFI (excluding respiratory and diarrheal causes), scrub typhus accounted for 10.5%, followed by malaria and typhoid; mortality reached 10.1% in the cohort [11]. These trends are consistent with a large serological study in Kolkata involving over 1,700 patients, which documented dengue (38.3%), leptospirosis (25%), scrub typhus (23.9%), and malaria (12.6%); notable complications included thrombocytopenia in dengue and meningoencephalitis in scrub typhus [12].

Clinical symptoms of AFI are often overlapping and non-specific. Common presentations include fever, headache (≈70–90%), myalgia, nausea/vomiting, and abdominal pain [12,13]. Complications vary by etiology as depicted in Table 1: dengue frequently causes hypovolemic shock, liver dysfunction, and bleeding; leptospirosis may lead to renal impairment and respiratory distress; scrub typhus can present with neurological manifestations including seizures [12,13].

Seasonality plays a key role in disease distribution. Dengue and scrub typhus cases peak during the monsoon and post-monsoon seasons; enteric fever and leptospirosis prevalence also correlates with rainfall and waterlogging. Despite targeted testing, up to 30% of AFI cases remain undiagnosed, underscoring the limitations of conventional diagnostics [8,9].

Table 1: Etiological Agents of Acute Febrile Illness in Indian Tertiary Care Hospitals—Prevalence and Distinguishing Clinical Features

S. No.	Etiological Agent	Reported Prevalence	Distinguishing Clinical Features	Reference
1	Dengue virus	23.0% – 43.5%	High-grade fever, rash, retro-orbital pain, thrombocytopenia, bleeding tendency, hepatic dysfunction	[8,9,12]
2	Scrub typhus (Orientia tsutsugamushi)	23.9% – 47%	Fever, eschar at bite site, lymphadenopathy, hepatosplenomegaly, altered sensorium, seizures	[8,12,13]
3	Leptospirosis	12.4% – 25%	Fever, myalgia (especially calf), conjunctival suffusion, jaundice, renal dysfunction, hemorrhagic symptoms	[8,12]

4	Enteric (typhoid) fever (Salmonella typhi/paratyphi)	4% – 15%	Step-ladder fever, abdominal pain, coated tongue, relative bradycardia, splenomegaly	[9,12]
5	Malaria (Plasmodium falciparum/vivax)	12% – 12.6%	Intermittent fever with chills, anemia, splenomegaly, altered consciousness in severe cases	[12,13]
6	Undiagnosed/indeterminate cases	6.7% – 30%	Non-specific fever, myalgia, malaise, no definitive lab findings	[8,9]

Conventional Diagnostic Approaches

In Indian tertiary care settings, acute febrile illness (AFI) is primarily investigated using conventional pathogen-specific tools such as microscopy, serological assays, and rapid diagnostic tests, as shown in Figure 1. Although widely available, many of these tools have limitations in sensitivity, specificity, or timeliness (refer Table 2), especially in resource-constrained regions.

Table 2: Showing Common Diagnostic Modalities in AFI

S. No.	Diagnostic Tool	Target Disease	Advantages	Limitations	Reference
1	Peripheral Blood Smear	Malaria	Gold standard, economical	Low sensitivity in low parasitemia, operator-dependent	[14]
2	Malaria RDT (HRP2/pLDH)	Malaria	Quick results, easy to use	Cannot quantify parasite load	[14]
3	NS1 + IgM ELISA	Dengue	High specificity, early detection	Moderate sensitivity (NS1 alone)	[14]
4	IgM ELISA (Scrub Typhus)	Scrub Typhus	High diagnostic accuracy	Requires ELISA setup	[15]
5	Weil–Felix Test (WFT)	Scrub Typhus, Rickettsial	Widely available, inexpensive	Low sensitivity and specificity	[14]
6	Widal Test	Typhoid Fever	Accessible, affordable	Cross-reactivity, low diagnostic value in endemic areas	[14]
7	Blood Culture	Typhoid Fever	Definitive diagnosis	Time-consuming, requires infrastructure	[1]

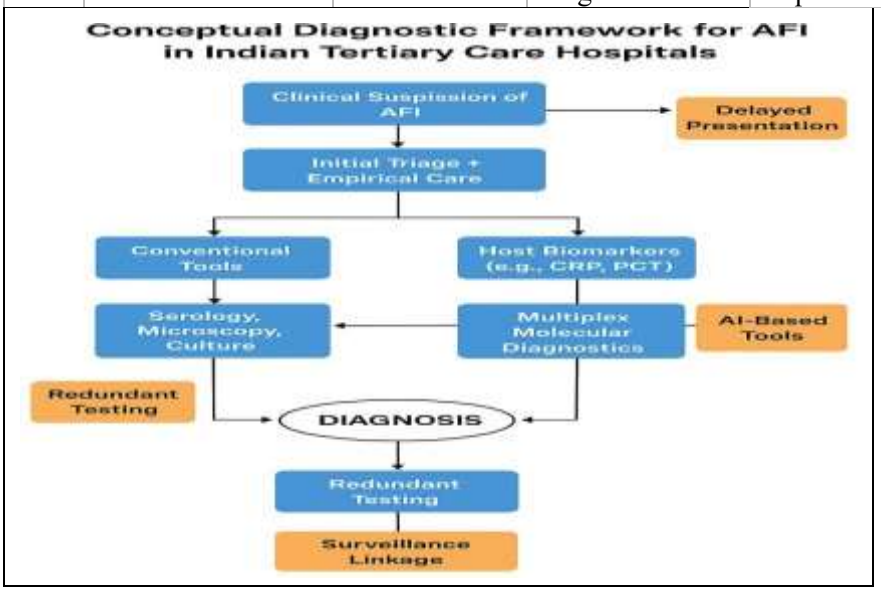

Figure 1: Conceptual Diagnostic Framework for Acute Febrile Illness in Indian Tertiary Care Hospitals

Emerging Biomarkers & Diagnostic Tools

Advancements in host biomarkers, point-of-care (POC) diagnostics, and multiplex platforms are transforming the diagnostic approach for acute febrile illness (AFI) as mentioned in Table 3, especially in settings facing co-endemic infections and limited lab infrastructure [16].

1. Host Biomarkers

C-Reactive Protein (CRP) and Procalcitonin (PCT) have emerged as valuable adjuncts in distinguishing bacterial infections from viral or parasitic etiologies. CRP generally outperforms PCT, with higher AUROC values in tropical fever settings (AUROC ≈ 0.83 vs 0.74) (WHO regions in Cambodia study) [17].

An Indian study of febrile neutropenia patients found CRP (>160 mg/dL at 48 h) achieved 100% sensitivity, while PCT at 24 h had 87.5% specificity for identifying fungal versus bacterial fever [5].

In critically ill adults with nosocomial fever, both biomarkers showed limited standalone utility (PCT AUC = 0.61; CRP AUC = 0.45), emphasizing need for combined clinical algorithms [18].

Recent tertiary ICU research linked serial trends of CRP, PCT, and neutrophil CD64 levels with prognostication in sepsis/septic shock [19,20].

2. Point-of-Care & Multiplex Diagnostic

CRP POC tests, integrated with existing RDT frameworks (e.g., malaria), offer low-cost, rapid differentiation of bacterial vs viral fevers. Models estimate CRP POC use could reduce inappropriate antibiotic prescriptions in malaria-endemic areas [17,21]. Low-cost Microfluidics and lab-on-chip biosensors—including graphene-based and cartridge RT-PCR platforms—can support emerging multiplex detection of multiple pathogens simultaneously. These tools offer ultra-sensitive, rapid (within minutes) detection suitable for low-resource settings [22,23].

Table 3: Emerging Diagnostic Tools for Acute Febrile Illness

Tool / Approach	Targeted Use	Key Benefits	Limitations	Reference
CRP point-of-care test	Differentiating bacterial vs viral/parasitic fevers	Affordable; rapid; integrates with existing RDTs	Cannot identify specific pathogens	[17]
Procalcitonin & CRP with clinical algorithm	AFI prognosis and antimicrobial stewardship	Moderate accuracy; guides antibiotic decisions	Best as part of algorithm, not stand-alone	[18]
Serial CRP, PCT, neutrophil CD64	Prognostic monitoring in sepsis/ICU	Correlates with severity; helps treatment planning	Resource-intensive; limited to ICU context	[19]
Lab-on-chip / biosensor multiplex assays	Simultaneous detection of multiple pathogens	Ultra-sensitive; quick turnaround; minimal training	Emerging tech; limited clinical validation	[22,23]

Challenges in the Indian Context

The diagnostic evaluation of acute febrile illness (AFI) in India is complicated by a diverse spectrum of infectious etiologies, frequent co-infections, and limitations in diagnostic infrastructure. These challenges are compounded in tertiary care hospitals that serve as referral centers for rural and underserved populations.

1. Resource Constraints and Infrastructure Gaps

Many tertiary hospitals in India lack adequate point-of-care (POC) testing facilities, rapid diagnostics, and trained personnel, particularly in high-burden government centers. Turnaround times for confirmatory tests (e.g., blood cultures, ELISA) often exceed 48–72 hours, resulting in delays in targeted therapy [3]. In the absence of rapid diagnostics, empirical treatment—often with broad-spectrum antibiotics—is initiated, contributing to antimicrobial resistance [24].

2. Overlapping Clinical Presentations

The non-specific symptomatology of AFI—fever, myalgia, headache, rash, gastrointestinal upset—makes clinical diagnosis difficult without laboratory confirmation. Diseases such as dengue, malaria, leptospirosis, scrub typhus, and typhoid fever share overlapping features, especially during monsoon and post-monsoon seasons. In a multi-centre cohort study, up to 30% of AFI cases remained undiagnosed even after extensive serological and parasitological workup [9].

3. Diagnostic Redundancy and Cost Burden

In many centers, patients undergo multiple redundant tests, including overlapping serological panels (e.g., Widal, Weil–Felix, NS1, IgM ELISA) without algorithmic prioritization. This increases the financial burden on both the healthcare system and the patient, particularly in out-of-pocket payment models [14]. Additionally, these tests often lack specificity, leading to false positives and inappropriate treatments.

4. Inconsistent Diagnostic Algorithms

There is no standardized diagnostic algorithm adopted across tertiary care institutions in India. Practices vary widely based on clinician preference, test availability, and regional epidemiology. As a result, diagnostic stewardship is weak, and decision-making is fragmented, especially in the early stages of hospitalization [3,24].

5. Seasonal and Geographic Variation

The epidemiology of AFI is highly region- and season-specific, yet most hospitals use generic fever panels throughout the year. For example, dengue and scrub typhus peak during monsoon months, while malaria may be prevalent year-round in endemic belts. A lack of dynamic, regionally-adapted diagnostic protocols leads to underdiagnosis of certain pathogens [8].

Opportunities and Innovations

To address the complex diagnostic landscape of acute febrile illness (AFI) in Indian tertiary care hospitals, a range of implementation-focused innovations are emerging. These strategies emphasize system-level improvements, local manufacturing, and clinical decision integration rather than isolated test development. Figure 2 illustrates a stepwise framework integrating diagnostic innovations with enabling systems. It emphasizes scalable mechanisms to drive improved diagnostic accuracy, faster treatment initiation, and optimized antimicrobial use in Indian tertiary care settings.

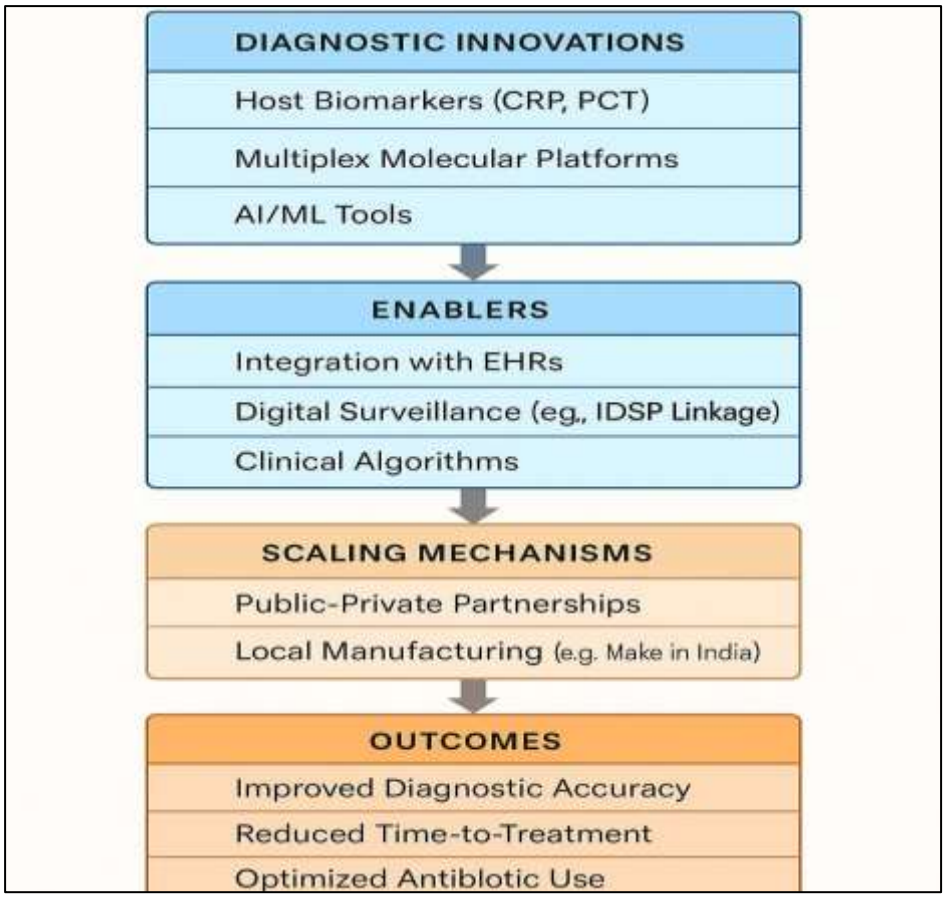

Figure 2: Innovation Landscape and Implementation Pathway for Acute Febrile Illness Diagnostics

1. Algorithm-Driven Biomarker Integration

While CRP and PCT are well-studied, their real-world value lies in structured integration into tiered clinical algorithms. Programs in Southeast Asia have demonstrated that using CRP thresholds to guide empirical antibiotic use can substantially reduce overtreatment. Embedding these biomarkers into digital triage tools or clinical checklists may enhance diagnostic stewardship in Indian settings [17].

2. Adaptive Multiplex Platforms for Tertiary Hospitals

Rather than discussing their diagnostic capabilities, the focus here is on implementation potential. Repurposing platforms like GeneXpert or TrueNat, already established for tuberculosis, offers a cost-effective route to introduce multiplex AFI testing. This approach leverages existing infrastructure and logistics networks, minimizing new investments [23].

3. AI and Clinical Decision Support

Emerging AI algorithms trained on local clinical and epidemiologic data are being piloted in urban tertiary centers. These tools assist clinicians by predicting probable etiology based on regional trends and patient inputs, thereby aiding early decision-making. Pilot studies in North India have shown promising results in reducing diagnostic delays and improving targeted therapy [8,26].

4. Surveillance-Integrated Diagnostics

Diagnostic platforms linked with real-time disease surveillance systems (e.g., IDSP) can alert clinicians to ongoing regional outbreaks. Hospitals can dynamically adjust diagnostic panels based on this data, improving seasonal sensitivity and public health responsiveness [3].

5. Policy-Level Innovations and Local Manufacturing

National health missions and make in India initiatives have led to the development of low-cost, high-volume RDTs for diseases like dengue and typhoid [27]. These innovations must now be accompanied by standardized diagnostic algorithms and cross-sector collaborations to ensure effective uptake in tertiary care workflows.

Research Gaps and Future Directions

Despite advancements in diagnostics, the management of acute febrile illness (AFI) in Indian tertiary care settings remains hindered by significant research and implementation gaps. Addressing these gaps is essential for developing context-appropriate, evidence-based, and scalable diagnostic strategies.

1. Lack of Validated Diagnostic Algorithms for Co-Endemic Settings

There is a pressing need for region-specific, algorithm-based diagnostic protocols that account for India's co-endemicity of dengue, scrub typhus, typhoid, leptospirosis, and malaria. Existing algorithms are often adapted from Western or WHO frameworks without adequate validation in Indian epidemiological contexts. Multicentric prospective studies are required to develop and validate diagnostic scoring systems tailored to Indian tertiary hospitals [28].

2. Limited Data on Biomarker Utility Across Fever Syndromes

Although biomarkers such as CRP, PCT, and CD64 show promise, their diagnostic and prognostic roles remain underexplored across diverse fever etiologies beyond sepsis [25]. Research is needed to understand their kinetics, diagnostic thresholds, and utility across different AFI syndromes such as rickettsial infections, enteric fever, and mixed infections.

3. Inadequate Evaluation of Multiplex and Syndromic Platforms

Many biosensor and multiplex diagnostics are still in preclinical or pilot phases, with insufficient validation in India's public health settings. Large-scale implementation science trials are needed to assess their clinical value, cost-effectiveness, and diagnostic accuracy [29].

4. Absence of Seasonally Adaptive Testing Models

Despite strong seasonal variation in AFI epidemiology, hospitals continue using uniform fever panels throughout the year. Few studies have evaluated dynamic, climate-informed diagnostic algorithms that adjust based on meteorological or surveillance data [28].

5. Fragmented Surveillance and Data Integration

Although platforms like the Integrated Disease Surveillance Programme (IDSP) exist, real-time integration of clinical, diagnostic, and epidemiologic data remains fragmented [31]. Research into EHR-linked dashboards, AI-driven alerts, and data harmonization frameworks is necessary to bridge diagnostics and surveillance [30].

CONCLUSION

The diagnosis of acute febrile illness (AFI) in India's tertiary care hospitals continues to face multidimensional challenges—ranging from overlapping clinical syndromes and limited diagnostic specificity to infrastructure constraints and non-adaptive testing protocols. While conventional diagnostic approaches remain indispensable, they often fall short in co-endemic, resource-limited settings where delayed or inaccurate diagnosis can adversely affect clinical outcomes and fuel antimicrobial resistance. This review highlights promising innovations such as host biomarker-guided algorithms, multiplex and syndromic testing, AI-powered decision support tools, and locally manufactured point-of-care diagnostics.

These advances, if implemented alongside digital surveillance integration and region-specific diagnostic protocols, can bridge current diagnostic gaps and strengthen AFI management in India.

However, to translate these opportunities into clinical and public health gains, India-specific research must prioritize the validation of algorithms, contextual adaptation of technologies, and cross-sector collaborations for scalable deployment. Moving forward, a hybrid approach combining evidence-based clinical judgment with rapid, cost-effective diagnostics offers the most practical path toward improving the accuracy, efficiency, and timeliness of AFI diagnosis across India's tertiary healthcare landscape.

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